

Capsules

26.08.2023 // Reference: Ansel's Pharmaceutical Dosage Forms and Drug Delivery System 10th Edition

Objectives

- Differentiate between hard gelatin and soft gelatin capsules
- Compare and contrast advantages and disadvantages of hard gelatin and soft gelatin capsules
- List categories of inert ingredients, with examples, which are employed in the compounding or manufacture of capsules
- State USP compendia requirements for capsules
- Define and differentiate weight variation from content uniformity
- Describe appropriate techniques for compounding, inspecting, packaging and storing capsules

Capsules

- Are solid dosage forms in which medicinal agents and/or inert substances are *enclosed in a small shell of gelatin*.
 - Gelatin capsule shells may be *hard or soft*, depending on their composition.
- Intended to be swallowed whole; however, it is fairly common in hospitals/extended care facilities for a caregiver to open capsules or crush tablets to mix with food or drink especially for children or other patients unable to swallow solid dosage forms.

Hard Gelatin Capsules

- Are used in most commercial medicated capsules.
- Also commonly employed in clinical drug trials to compare the effects of an investigational drug with those of another drug product or placebo.
- Used in extemporaneous compounding of prescriptions.
 - Empty capsule shells are made of ***gelatin, sugar and water.***
 - Gelatin is obtained by the ***partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals***
 - ***Hydroxypropylmethylcellulose (HPMC) - gelatin coming from vegetable origin***
 - May be colored with various **FD&C and D&C dyes**
 - Made opaque by adding agents such as ***titanium dioxide***

Hard Gelatin Capsules

- Contain **13%-16% moisture**
- If stored in high humidity, additional moisture is absorbed by the capsules and they may become distorted.
- Extreme dryness: Capsules may become *brittle and crumble*
- Many capsules are packaged along with a small packet of dessicant material to protect against the absorption of atmospheric moisture
 - Dessicant most often used: **Dried silica gel, clay and activated charcoal**

The Manufacture of Hard Gelatin Capsule Shells

- Hard gelatin capsule shells are manufactured in two sections: the capsule body and a shorter cap.
- The shells are produced industrially by the *mechanical **dipping** of pins or pegs of the desired shape and diameter* into a temperature-controlled reservoir of melted gelatin mixture (fig. 7.3)
- The pegs, made of **manganese bronze**, affixed to plates, each capable of holding up to about 500 pegs.

The Manufacture of Hard Gelatin Capsule Shells

- Each plate is **lowered into the gelatin bath**
- Submerged to the **desired depth and maintained for the desired period to achieve the proper length and thickness of coating.**
- Then the plate and pegs are **slowly lifted** from the bath and the gelatin is **dried by a gentle flow of temperature and humidity-controlled air**

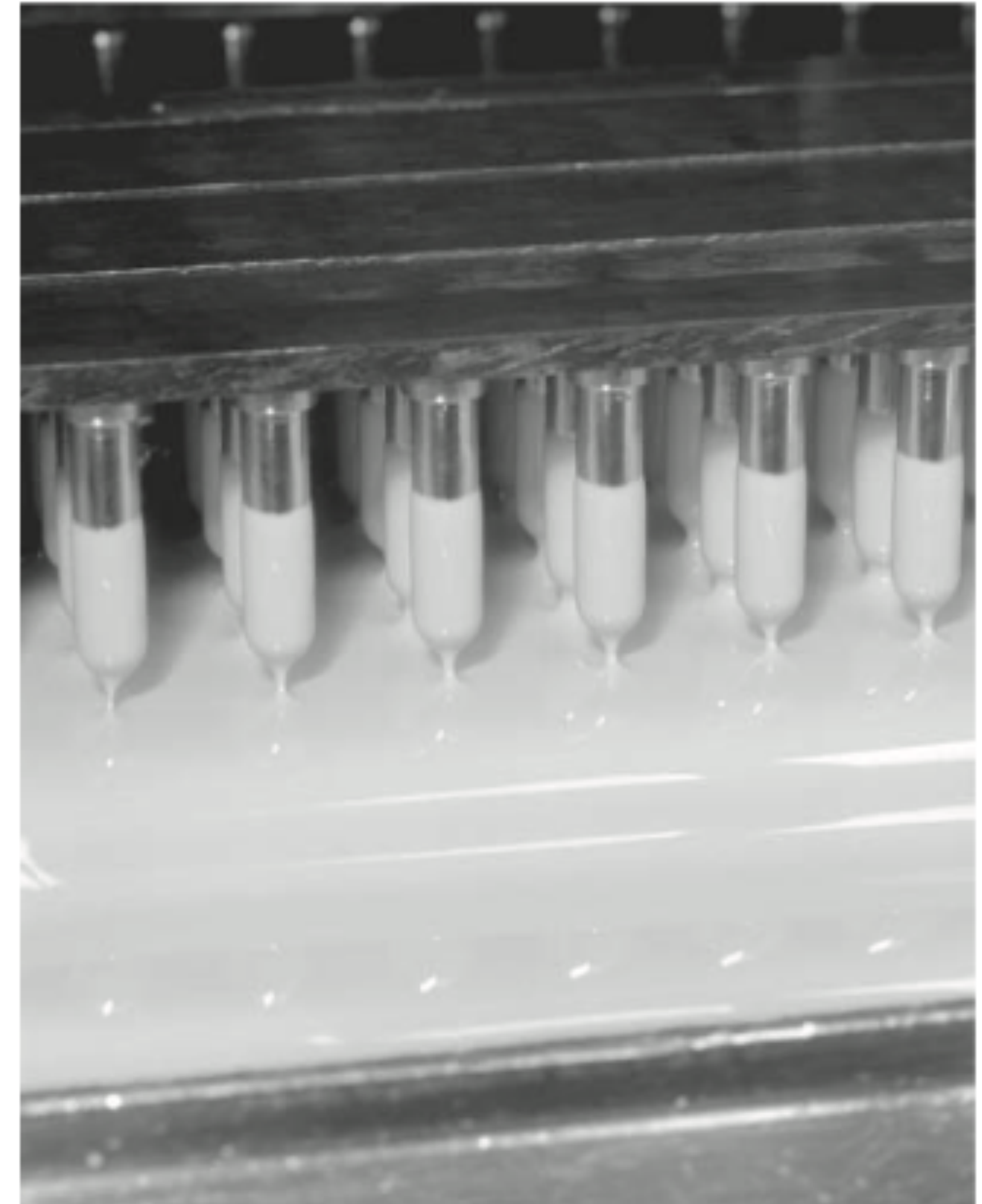


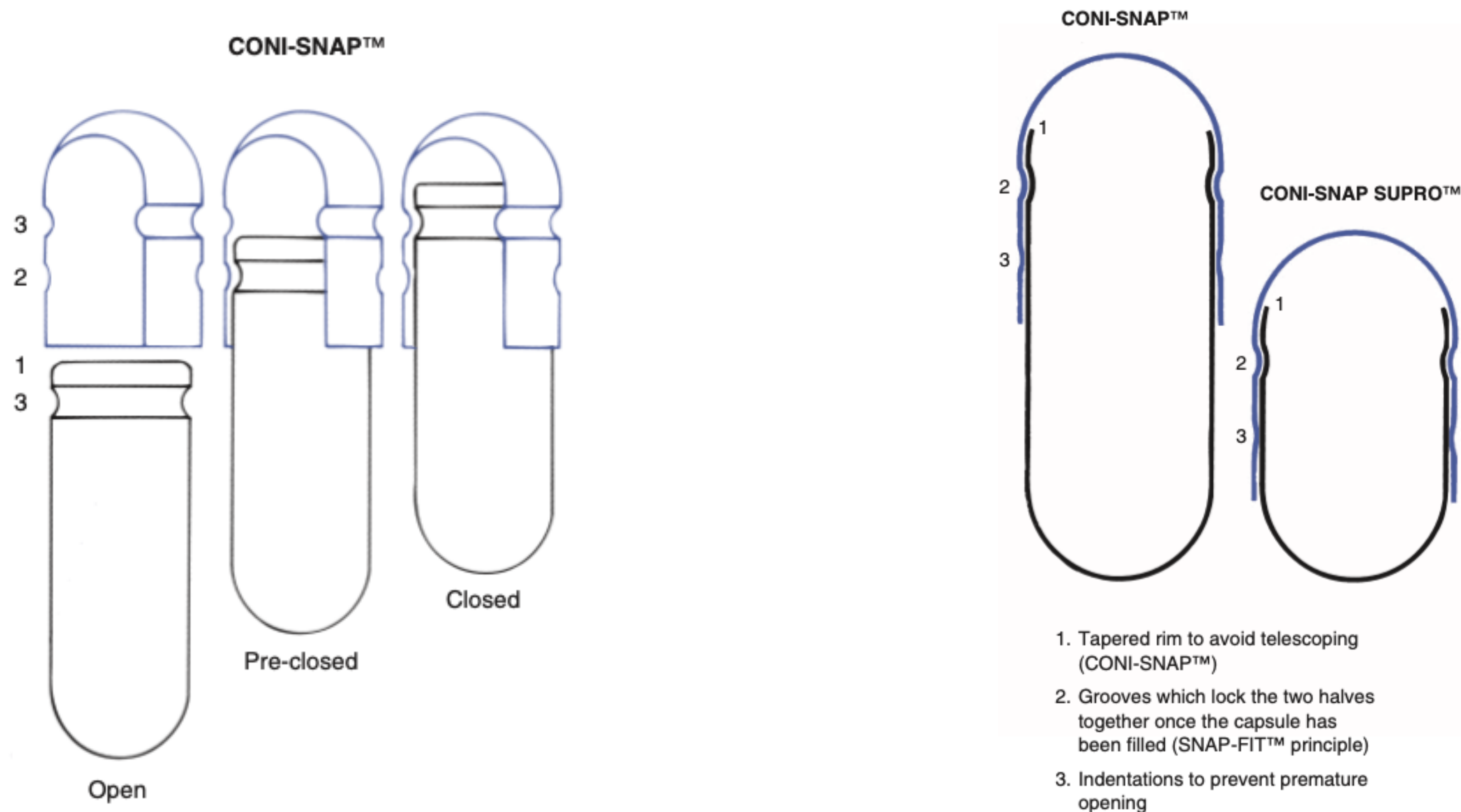
FIGURE 7.3 Capsules being dipped for coloring on automated capsule-making equipment. (Courtesy of Shinogi Qualicaps.)

The Manufacture of Hard Gelatin Capsule Shells

- When dried, each capsule part is **trimmed** mechanically to the proper length and removed from the pegs, and the capsule bodies and caps are **joined together**.
- Important: The thickness of the gelatin walls **must be strictly controlled** so that the capsule's body and cap fit snugly to prevent disengagement.
- There is a **continuous** dipping, drying, removing and joining of capsules as the peg-containing plates rotate in and out of the gelatin bath.

The Manufacture of Hard Gelatin Capsule Shells

- A manufacturer also may prepare distinctive-looking capsules by altering the usual rounded shape of the capsule-making pegs. // by tapering



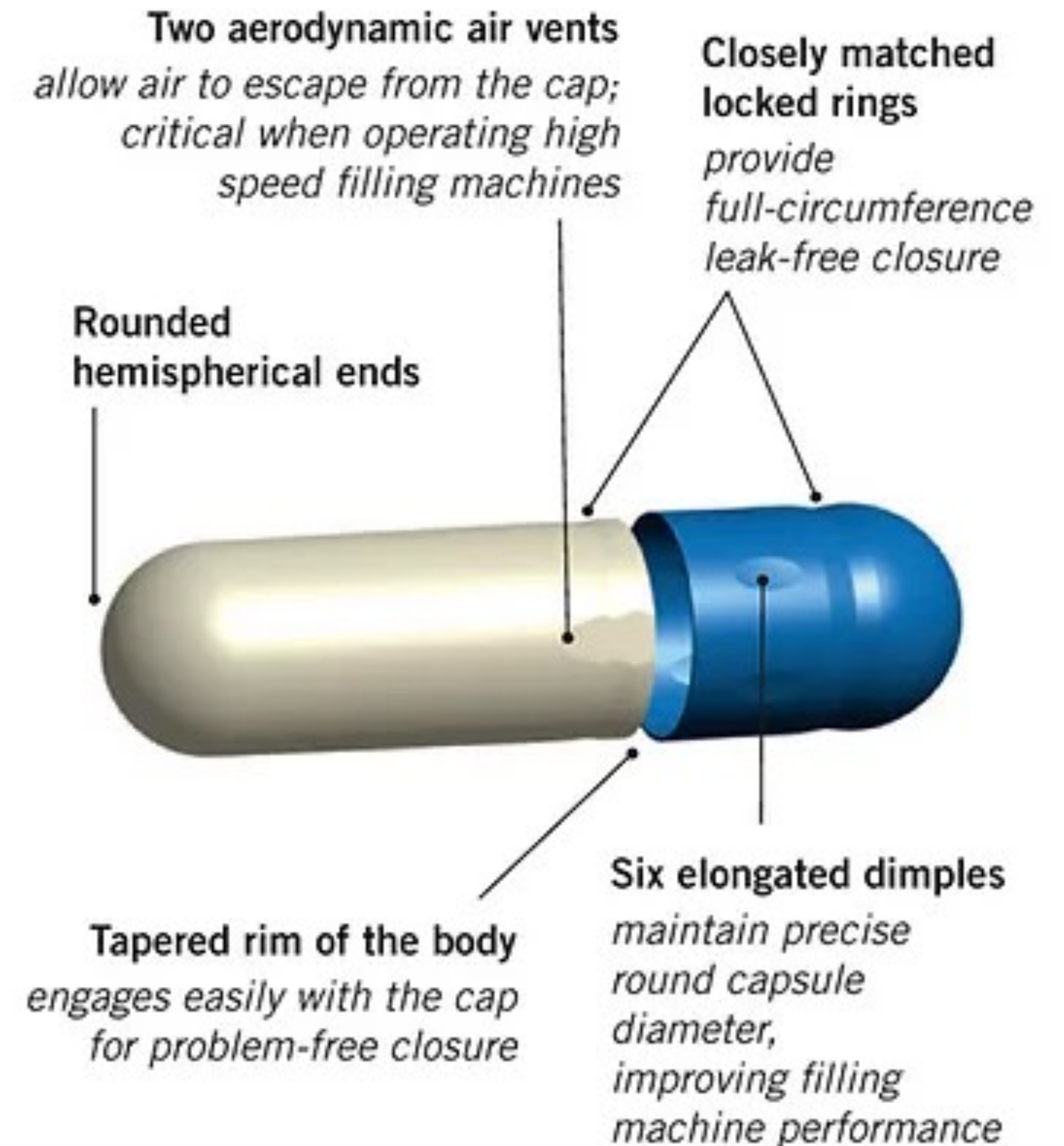
The Manufacture of Hard Gelatin Capsule Shells

- Coni-snap
- Coni-snap Supro
- Snap-fit
- Spansule capsule

*some manufacturers render their capsules tamper evident through various sealing techniques.

*capsules and tablets also may be imprinted with the names or monograms of the manufacturer.

Coni-Snap® capsules - Designed to Perform



Capsule sizes

- Are manufactured in various lengths, diameters and capacities.
- The size selected for use is determined by the amount of fill material to be encapsulated.
- The *density and compressibility* of the fill will largely determine to what extent it may be packed into a capsule shell (fig. 7.6)
- For *estimation*, a comparison may be made with powders of well-known features (fig. 7.1) and an *initial judgment is made* as to the approximated capsule size needed to hold a specific amount of material.
- However, the *final determination may be largely the result of trial and error*

Capsule sizes

TABLE 7.1 APPROXIMATE CAPACITY OF EMPTY GELATIN CAPSULES

	CAPSULE SIZE							
	000	00	0	1	2	3	4	5
Volume (mL)	1.40	0.95	0.68	0.50	0.37	0.30	0.21	0.13
Drug substance (mg) ^a								
Quinine sulfate	650	390	325	227	195	130	97	65
Sodium bicarbonate	1430	975	715	510	390	325	260	130
Aspirin	1040	650	520	325	260	195	162	97

^aAmount may vary with the degree of pressure used in filling the capsules.

Capsule sizes

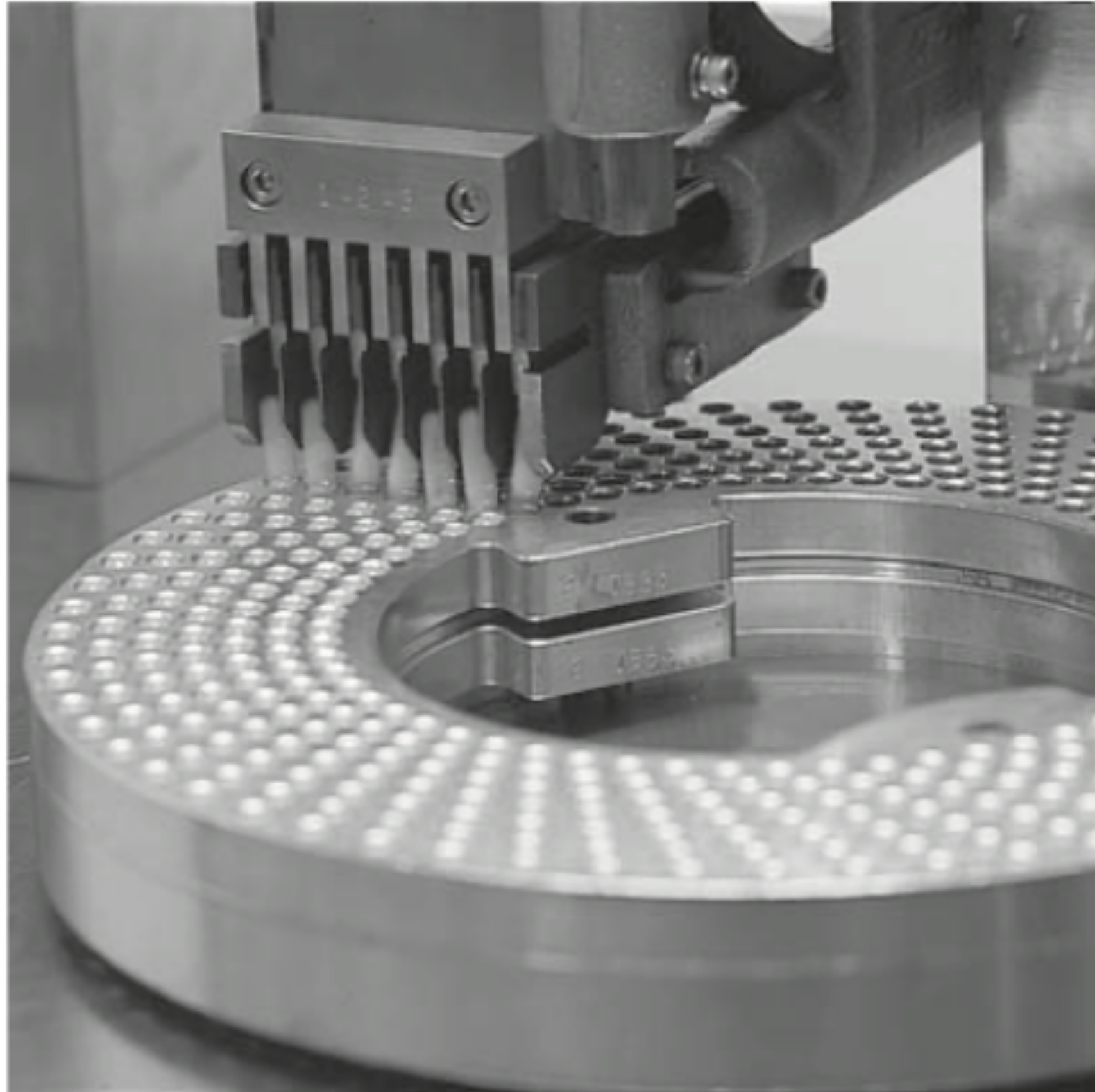
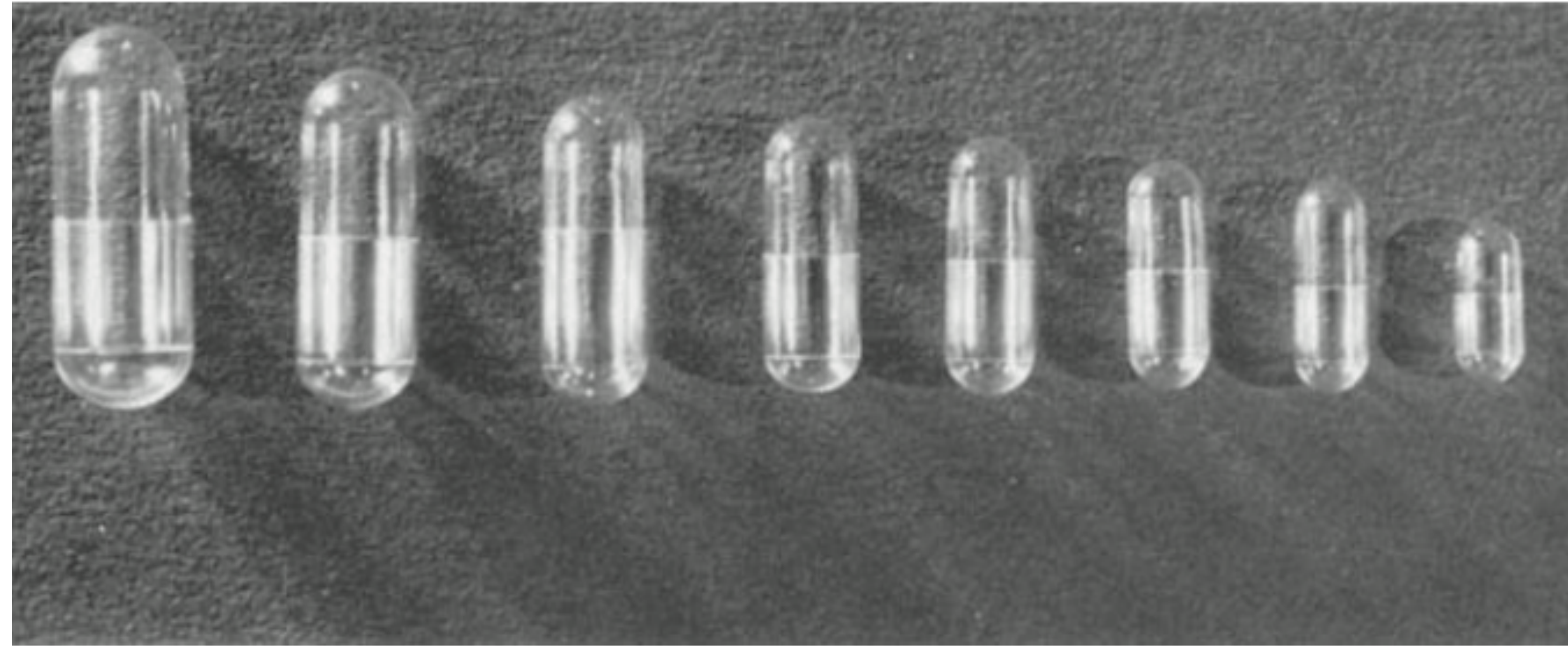


FIGURE 7.6 Capsule ring containing capsule halves being filled with powder. (Courtesy of Shinogi Qualicaps.)



ual sizes of hard gelatin capsules. From left to right, sizes 000, 00, 0, 1, 2, 3, 4, and 5.

Preparation of Filled Hard Gelatin Capsules

Large-scale/small-scale

Step 1: Developing and preparing the formulation and selecting the capsule size

Step 2: Filling the capsule shells

Step 3: Capsule sealing (optional)

Step 4: Cleaning and polishing the filled capsules

Developing the formulation and selecting the capsule size

- Active and inactive components must be blended thoroughly to ensure a uniform powder mix for the fill
- A **diluent or filler** may be added to produce the proper capsule volume.
 - Examples: **lactose, microcrystalline cellulose, starch**
 - In addition to providing bulk, these materials often provide cohesion to the powders, which is beneficial in the transfer of the powder blend into capsule shells.

Developing the formulation and selecting the capsule size

- Disintegrants - are frequently included in a capsule formulation to assist breakup and distribution of the capsule's contents in the stomach
 - Examples: **pregelatinized starch, croscarmellose, and sodium starch glycolate**
 - Note: to achieve uniform drug distribution, it is advantageous if the density and particle size of the drug and nondrug components are similar.
 - Particle size may be reduced by **milling** to produce particles ranging from about **50 to 1000 microns**.
 - **Micronization** - produces particles **1-20 microns**.

Developing the formulation and selecting the capsule size

- Lubricant - makes powders **free-flowing** to allow steady passage of the capsule fill from the hopper through the encapsulating equipment and into the capsule shells
 - Enhances flow properties
 - Examples: Fumed silicon dioxide, magnesium stearate, calcium stearate,, stearic acid, or talc (about 0.25% to 1%)

Developing the formulation and selecting the capsule size

- When magnesium stearate (water-insoluble/has waterproofing characteristics) is used as a lubricant, it can *retard penetration* by the gastrointestinal fluids and *delay drug dissolution and absorption*
 - a surface active agent such as **sodium lauryl sulfate (SLS)** is used to facilitate wetting by the gastrointestinal fluids to overcome the problem

Developing the formulation and selecting the capsule size

Capsules are use for filling different materials like



Powder



Granules



Beads



Tablets



Caplets



Pastes



Developing the formulation and selecting the capsule size

- Considerations in selecting the capsule size:
 - Dose of the active ingredient
 - Density of powder
 - Compaction characteristics (capsule-filling machine)
- Hard gelatin capsules are used to encapsulate about 65 mg to 1 gram of powdered material.

Developing the formulation and selecting the capsule size

- Selecting the capsule size

Step 1: Weigh the ingredients for the required number of capsules to be prepared

Step 2: Place the powders in a graduated cylinder

Step 3: Obtain the volume occupied by the powders

Step 4: Divide the volume by the number of capsules to be prepared

Step 5: This provides the volume that will be occupied by the powder for each capsule

Step 6: Compare this volume (in mL) with the appropriate line of Table 7.1

Capsule sizes

TABLE 7.1 APPROXIMATE CAPACITY OF EMPTY GELATIN CAPSULES

	CAPSULE SIZE							
	000	00	0	1	2	3	4	5
Volume (mL)	1.40	0.95	0.68	0.50	0.37	0.30	0.21	0.13
Drug substance (mg) ^a								
Quinine sulfate	650	390	325	227	195	130	97	65
Sodium bicarbonate	1430	975	715	510	390	325	260	130
Aspirin	1040	650	520	325	260	195	162	97

^aAmount may vary with the degree of pressure used in filling the capsules.

Capsule Sizes

Example:

- Ferrous Sulfate - 200 mg x 5 capsules = 1000 mg
- Lactose - 350 mg x 5 capsules = 1750 mg

Total weight: 2750 mg or 2.76 grams

- $2 \text{ ml} \div 5 \text{ capsules} = 0.4 \text{ mL}$



Filling hard capsule shells

1. Punch method

- The amount of powder packed into a capsule depends on the degree of compression, the pharmacist should punch each capsule in the same manner and weigh the product after capping.
- Capsules should be prepared and weighed periodically to check the uniformity of the process.
 - Such weighings protect against uneven filling of capsules

Filling hard capsule shells

2. Capsule filling machine (Feton)

- Hand-operated filling machine
- Have capacities ranging from 24-300 capsules and when efficiently operated are capable of producing about 200-2000 capsules per hour

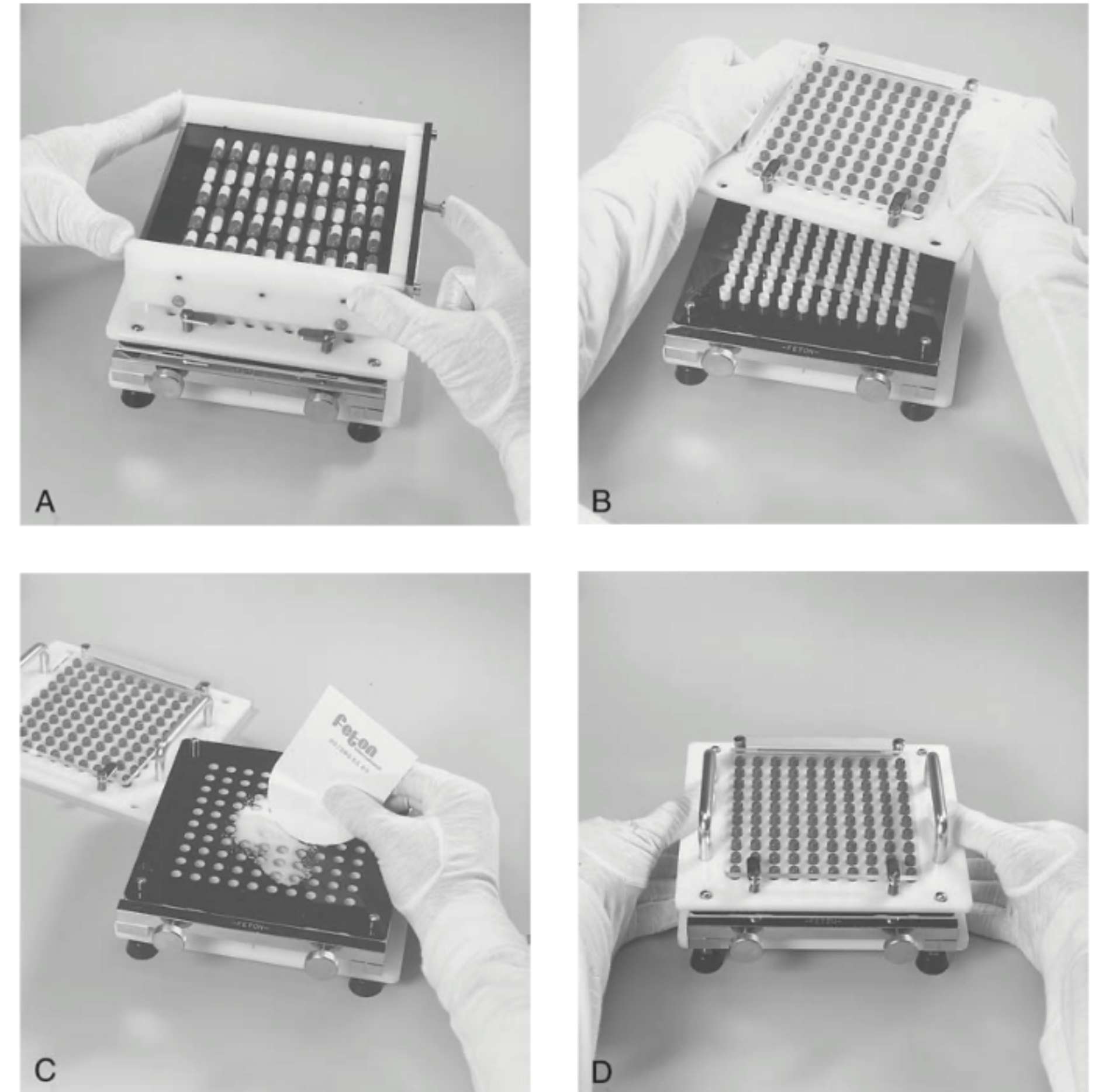


FIGURE 7.9 The Feton capsule-filling machine. **A.** With empty capsules in the loader tray, the tray placed on top of the filler unit. **B.** The loader inserts the capsules into the filling unit and is removed, and the top plate is lifted to separate the caps from the bodies. **C.** The powder is placed on the unit and the capsule bodies are filled. **D.** The top plate is returned to the unit and the caps are placed on filled capsule bodies. (Courtesy of Chemical and Pharmaceutical Industry Company.)

Prepare your equipment...



*Sold separately

Filling hard capsule shells

3. Osaka Automatic Capsule Filler model

- Industrial use
- Automatically separate the caps from empty capsules, fill the bodies, scrape off excess powder, replace the caps, seal the capsules as desired
- 165,000 capsules per hour

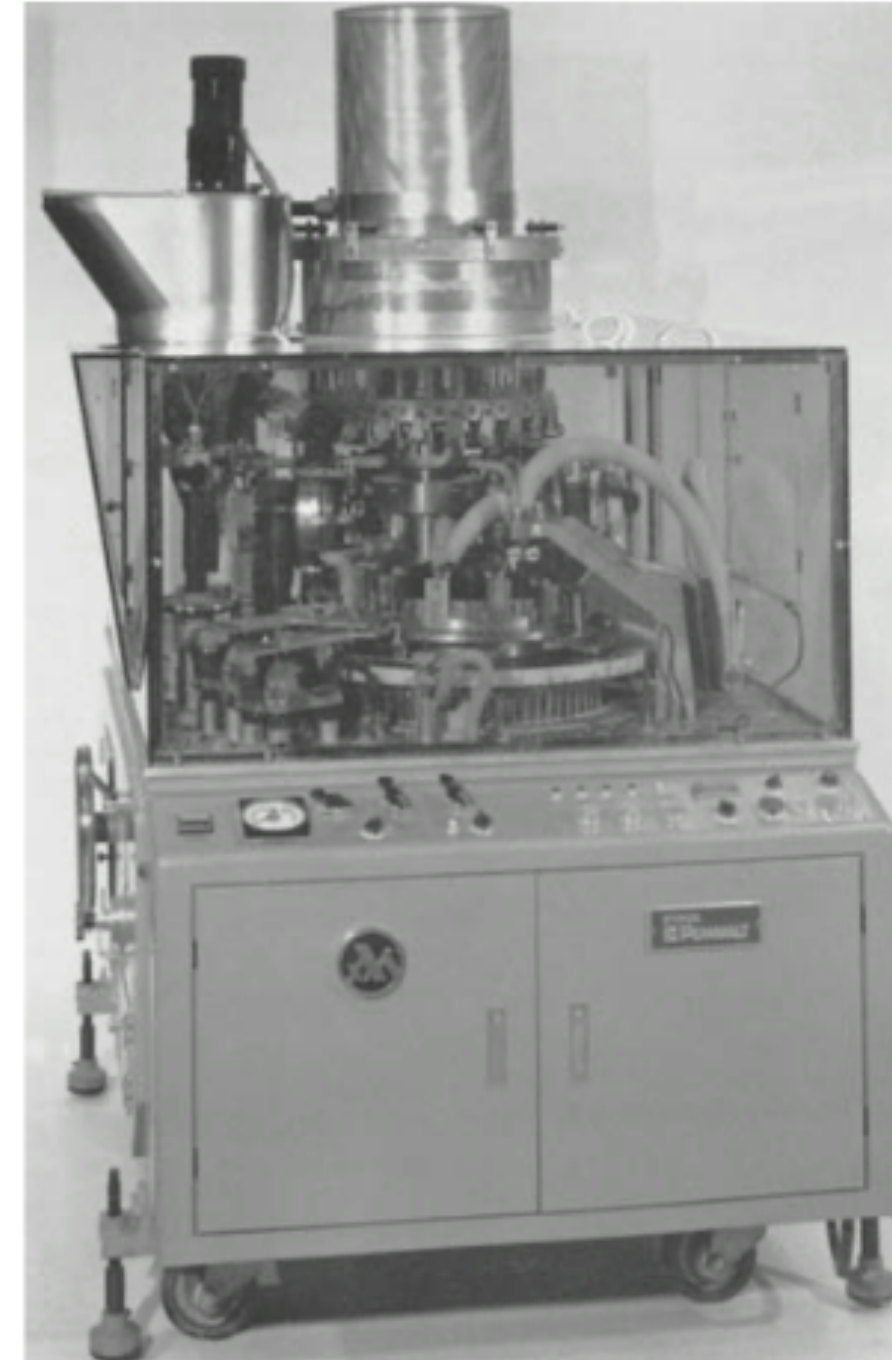


FIGURE 7.10 Osaka Automatic Capsule Filler model R-180, capable of filling up to 165,000 capsules per hour. (Courtesy of Sharples-Stokes Division, Stokes-Merrill, Pennwalt Corporation.)



Capsule sealing

- Manufacturers make distinctive-looking capsules by sealing them with a:
 - Colored band of gelatin (Kapseals, Parke-Davis)
 - Heat-welding process - fuses the capsule cap through the double wall thickness at their juncture
 - Usage of a *liquid wetting agent* that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures.

Capsule sealing



FIGURE 7.14 Z-Weld's gelatin seal fuses the two capsule halves to create a one-piece capsule that is tamper evident. (Courtesy of Raymond Automation.)



STAGE 1 Spraying

Sealing fluid is sprayed onto joint between cap and body.

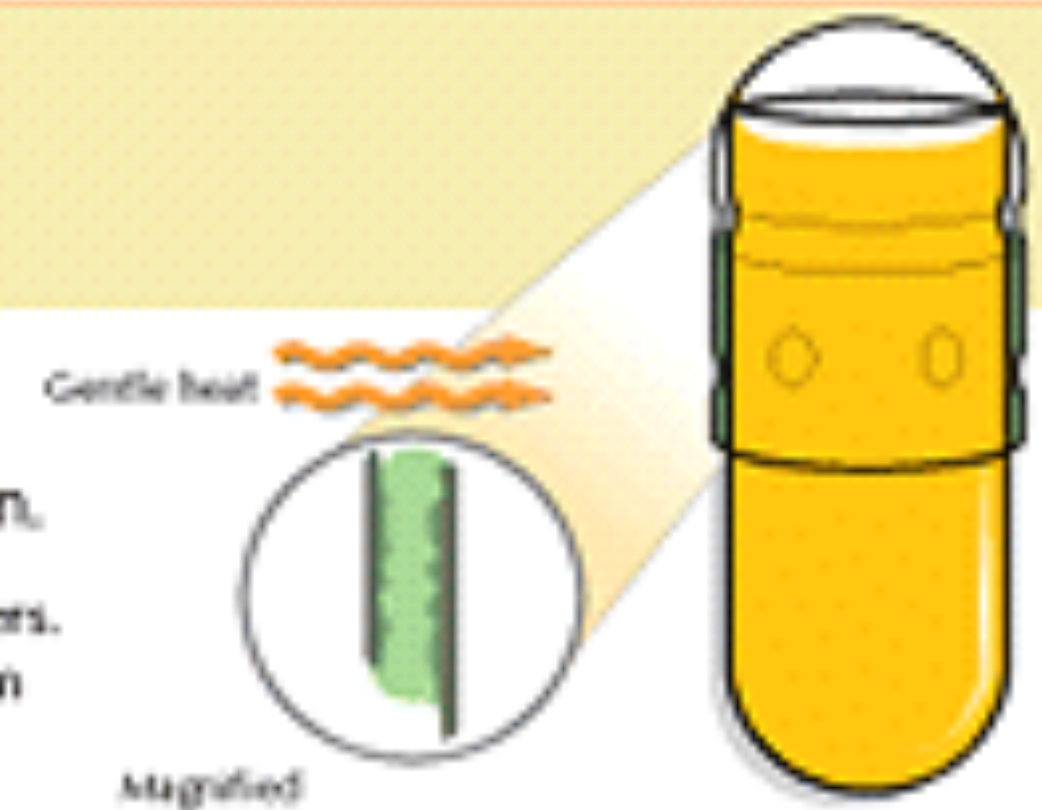
Capillary action draws fluid up between the cap and the body. Suction removes excess fluid.



STAGE 2 Warming

A gentle heat application completes melting and fusion.

Gentle heat melts the two shell layers. The two layers fuse together to form an impervious seal.



STAGE 3 Setting

The polymer sets and hardens at room temperature.

Finishing of capsules

- Cloth dusting - capsules are rubbed with cloth
- Polishing - Accela-Cota pan is used to dust and polish using a polyurethane cloth
- Brushing - Capsules are feed under soft rotating brush.



FIGURE 7.15 Cleaning and polishing hard-filled capsules using the Accela-Cota apparatus. (Courtesy of Eli Lilly and Company.)

Soft Gelatin Capsules

- Are made of gelatin to which glycerin or a polyhydric alcohol such as **sorbitol** has been added.
- Contain more moisture than hard capsules, may have a preservative such as methylparaben and/or propylparaben, to retard microbial growth.
- They may be single colored or two toned and may be imprinted with identifying markings.
- They may be prepared with opacifiers
- Are used to encapsulate and hermetically seal liquids, suspensions, pasty materials, dry powders, and even preformed tablets.
- Are pharmaceutically elegant and easily swallowed.

Soft Gelatin Capsules

Preparation

1. Plate process

- using a *set of molds* to form the capsules

Step 1: a warm sheet of plain or colored gelatin is placed on the bottom plate of the mold, and the medication-containing liquid is evenly poured on it.

Step 2: a second sheet of gelatin is carefully placed on top of the medication, and the top plate of the mold is put into place.

Step 3: pressure is then applied to the mold to form, fill and seal the capsules simultaneously.

Step 4: the capsules are removed and washed with a solvent harmless to the capsules.

Soft Gelatin Capsules

Preparation

2. Rotary Die Process

- A method developed by Robert P. Scherer in 1933
- Liquid gelatin flowing from an overhead tank is formed into *two continuous ribbons* by the rotary die machine and brought together between two rotating dies where the capsule are simultaneously filled, shaped, hermetically sealed and cut from the gelatin ribbon.

Soft Gelatin Capsules

Rotary Die Process

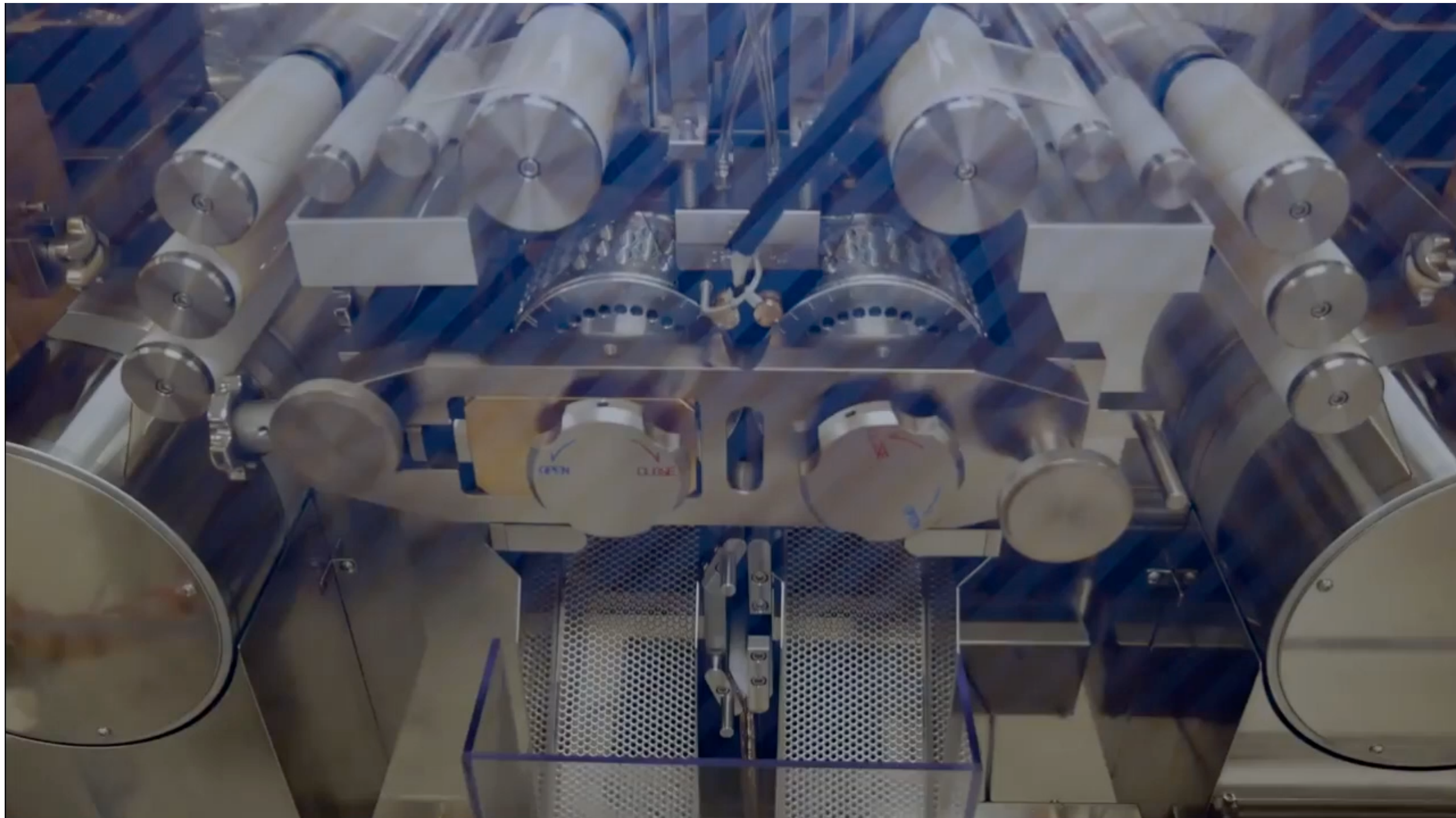
Softgel capsule machine



Rotary Die Process

Soft Gelatin Capsule

Manufacturing Process



Soft Gelatin Capsules

Preparation

3. Reciprocating Die Process

- Similar to rotary die process in that ribbons of gelatin are formed and used to encapsulate the fill, but it differs in the actual encapsulating process.
- The gelatin ribbons are fed between a set of ***vertical dies*** that continually open and close to form rows of pockets in the gelatin ribbons.
- These pockets are filled with the medication and are sealed, shaped and cut out of the film.
- As the capsules are cut from the ribbons, they fall into refrigerated tanks that prevent the capsules from adhering to one another.

Use of Soft Gelatin Capsules

- Soft gelatin capsules are prepared to contain a variety of liquid, paste, and dry fills.
1. Water-immiscible volatile and nonvolatile liquids: **vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols, and organic acids**
 2. Water-miscible nonvolatile liquids, such as **polyethylene glycols, and nonionic surface-active agents, such as polysorbate 80**
 3. Water-miscible and relatively nonvolatile compounds such as **propylene glycol and isopropyl alcohol**, depending on factors such as concentration used and packaging conditions.

Compendial Requirements for Capsules

1. Added Substances/excipients

- Are harmless in the quantities used
- Do not exceed the minimum amounts required to provide their intended effect
- Do not impair the product's bioavailability, therapeutic efficacy, or safety.
- Do not interfere with requisite compendial assays and tests

Compendial Requirements for Capsules

2. Containers for Dispensing Capsules

- Tight, well-closed, light resistant, and/or combination of these.

Compendial Requirements for Capsules

3. Dissolution Test

- Equipment used:
 - Speed stirrer motor
 - *A cylindrical stainless steel basket* on a stirrer shaft
 - *A 1Liter vessel of glass* fitted with a cover
 - *A water bath* to maintain the temperature of the dissolution medium in the vessel

Compendial Requirements for Capsules

3. Dissolution Test

Step 1. In each test, a volume of the dissolution medium is placed inside the vessel and allowed to come to $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$

Step 2. Then, the stirrer is rotated at the speed specified, and at stated intervals.

Step 3. Samples of the medium are withdrawn for chemical analysis of the proportion of the drug dissolved.

Step 4. The tablet or capsule must meet the stated monograph requirements for rate of dissolution (example: “not less than 85%, of the labeled amount is dissolved in 30 minutes”)

Compendial Requirements for Capsules

3. Disintegration Test

- Capsules are placed in a basket racket assembly
- Immersed 30 times per minute in a thermostatically controlled fluid (37c)
- Observed over time
- The capsules should disintegrate completely into a mass having no palpably firm core

Compendial Requirements for Capsules

4. Weight Variation

- Hard Capsules
 - 10 capsules are individually weighed and their contents removed. Emptied shells are individually weighed, and the net weight of the contents is calculated by subtraction.
- Soft Capsules
 - Gross weight of 10 capsules is determined individually; then each capsule is cut open, and the contents are removed by washing with a suitable solvent.
 - The solvent is allowed to evaporate at room temperature over about 30 minutes.
 - The individual shells are weighed and the net contents calculated.

Compendial Requirements for Capsules

5. Content Uniformity

- Unless otherwise stated in the USP monograph, the amount of active ingredient, determined by assay, is **within the range of 85%-115%** of the label claim for **9 of 10 dosage units** assayed, with no unit outside the range of 70% to 125% of the label claim

Compendial Requirements for Capsules

6. Stability Testing

- Stability of the active drug under the influence of environmental factors such as:
 - Temperature, humidity, light, container, and closure system.

Compendial Requirements for Capsules

7. Moisture Permeation Test

- The degree and rate of moisture penetration are determined by:
 - Packaging the dosage unit together with a color-revealing desiccant pellet
 - Exposing the packaged unit to known relative humidity over a specified time
 - Observing the desiccant pellet for color change (indicating the absorption of moisture)

Examples of some official capsules

Table 7.2 EXAMPLES OF SOME OFFICIAL CAPSULES

OFFICIAL CAPSULE	REPRESENTATIVE COMMERCIAL CAPSULES	STRENGTH (MG)	CATEGORY
Acyclovir	Various	200	Antiviral
Amoxicillin	Wymox (Wyeth-Ayerst)	250, 500	Antibacterial
Ampicillin	Omnipen (Wyeth-Ayerst)	250, 500	Antibacterial
Cephalexin	Keflex (Victory)	250, 333, 500, 750	Antibacterial
Diphenhydramine HCl	Benadryl (McNeil)	25	Antihistaminic
Docusate sodium	Various	250	Stool softener
Doxycycline hyclate	Vibramycin (Pfizer)	100	Antibacterial
Erythromycin estolate	Ilosone (Eli Lilly)	250	Antibacterial
Fluoxetine HCl	Various	10, 20, 40	Antidepressant
Flurazepam HCl	Various	15, 30	Hypnotic
Indomethacin	Indocin (Merck)	25, 50	Anti-inflammatory, antipyretic, analgesic
Loperamide HCl	Imodium (Janssen)	2	Antidiarrheal
Minocycline hydrochloride	Various	50, 75, 100	Antibacterial
Oxazepam	Various	10, 15, 30	Antianxiety
Paromomycin	Caraco Pharm Labs	250	Antiamoebic
Tetracycline HCl	Various	250, 500	Antibacterial
Vancomycin HCl	Vancocin (ViroPharma)	125, 250	Antibacterial
Zidovudine	Zidovudine (Aurobindo Pharma)	100	Antiretroviral

Examples of commercially prepared into soft gelatin capsules

Table 7.3 SOME MEDICATIONS COMMERCIALY PREPARED INTO SOFT GELATIN CAPSULES

DRUG	TRADE NAME (MANUFACTURER)	CONTENTS AND COMMENTS ^a
Acetazolamide	Diamox Sequels (Duramed)	Carbonic anhydrase inhibitor, slightly water-soluble powder. Contains coated pellets of sustained-release drug
Chloral hydrate	Various	Sedative-hypnotic
Cyclosporine	Sandimmune (Novartis)	Immunosuppressive, slightly water-soluble crystalline powder. Contains corn oil, polyoxyethylated glycolized glycerides
Cyclosporine	Neoral (Novartis)	Contains dehydrated alcohol; corn oil mono-, di-, and triglycerides; and polyoxyl 40 hydrogenated castor oil; forms microemulsion in contact with aqueous fluids for enhanced bioavailability
Docusate sodium	UDL	Stool softener-laxative
Ethosuximide	Zarontin (Parke-Davis)	Anticonvulsant, water-soluble powder. Contains polyethylene glycol 400
Ranitidine HCl	Zantac GELdose (Glaxo Wellcome)	Histamine H ₂ receptor inhibitor, water-soluble granular powder in nonaqueous matrix of synthetic coconut oil, triglycerides

^aOnly a partial listing of the capsule contents is given. The soft capsule shells may also contain colorants, opaquants, preservatives, and other agents.

Hard vs. Soft gelatin capsule

Sl. No.	Hard gelatin capsules	Soft gelatin capsules
01	The hard gelatin capsule shell consists of two parts: (a) Body; (b) Cap.	The soft gelatin capsule shell becomes a single unit after sealing the two halves of the capsules.
02	They are cylindrical in shape.	They are available in round, oval and tube like shapes.
03	The contents of a hard gelatin capsule usually consists of the medicaments or mixture of medicaments in the form of powder, beads or granules.	The contents of soft gelatin capsules usually consists of liquids or solids dissolved or dispersed in suitable excipients to give a paste-like consistency.
04	These are prepared from gelatin, titanium dioxide, coloring agent and plasticizer.	These are prepared from gelatin, plasticizer (Glycerin or Sorbitol) and a preservative.
05	Capsules are sealed after they are filled to ensure that the medicaments may not come out of the capsule due to rough handling.	Filling and sealing of soft gelatin capsules are done in a combined operation on machines.

Advantages vs. Disadvantages of Capsules

Advantage:

- Ease of use (easy to swallow)
- Suitable for substances having bitter taste and unpleasant odor
- Fewer excipients are required than tablets
- A high degree of flexibility to the formulation
- Economical than other dosage forms
- The gelatin shell can give protection of the drug from light
- A high degree of flexibility to the formulation

Advantages vs. Disadvantages of Capsules

Disadvantage:

- It may not be suitable for high-dose drugs
- When compared to tablets, the production speed is slower
- Not appropriate for highly efflorescent substances
- More costly in production compared to tablets
- Materials reactive with gelatin cannot be dispensed
- Large and crystal shape powders cannot be dispensed in capsules